
Drug Repurposing in Primary Healthcare: A review

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Abstract

The process of finding new medical indications for old drugs is known as drug repurposing or repositioning. As opposed to de novo drug discovery, drug repurposing strategies may be less costly, less time-consuming, and relatively safer. This process may be explained by common molecular pathways that contribute to many different diseases. Additionally, adverse effects of certain drugs may provide desirable effects in other disease states. The drug approval process may differ from one indication to another and between countries. Based on clinical trials and physicians' experiences, the use of off-label prescriptions is a common practice in medicine. Primary healthcare providers are gatekeepers for an efficient healthcare system as they face many challenges in managing patients with multiple comorbidities and polypharmacy. Repurposing certain drugs may be helpful to tackle these challenges. This review outlines the current most promising medications with potential multiple indications and their supporting evidence in primary healthcare.

Keywords: Multiple indications, primary health care, repositioning, repurposing, off-label.

Background

The pharmaceutical industry faces significant challenges as new drug discovery is decreasing, and the production of new agents is expensive and time-consuming⁽¹⁾. To overcome these challenges, a new approach emerged called drug repurposing or repositioning. With the process of drug repurposing/repositioning, new indications for current therapies can be identified and used to treat additional disease states⁽¹⁾. Drug repurposing has reduced safety risks as they have been thoroughly studied concerning their toxicity and possible side effects⁽²⁾. Regulatory agencies, such as the United States Food and Drug Administra-

tion (FDA) and the European Medicines Agency (EMA), are responsible for the approval of drugs for clinical use based on their safety and efficacy. Drug approval processes vary from one country to another, based on legislation⁽³⁾. Drugs can be approved (on-label) for one indication but may not be approved (off-label) for many other indications. These off-label prescriptions are common medicine practices, based on data from clinical trials and physicians' experience⁽⁴⁾. Primary healthcare is the cornerstone of any effective and efficient health care system, where accessible, continuous, coordinated, comprehensive, and accountable services are provided⁽⁵⁾. Multi-morbidity, the culture of single drug indication, and sub-

sequently polypharmacy is increasing challenges for primary care. The undesirable outcomes include adverse drug reactions, poor adherence, increased health service use, high costs and reduced quality of life⁽⁶⁾. Drug repurposing may be helpful to tackle these challenges. This review aims to discuss the most common drugs with multiple indications prescribed in the primary healthcare settings. *Methods:* Searching process was performed using different electronic databases including MEDLINE (via PubMed), EMBASE, Elsevier/ScienceDirect and Cochrane Central Register of Controlled Trials (CENTRAL). The searches were limited to articles evaluating medication-indication in outpatient clinics or primary health care only and published between 1986 and 2020. It was restricted only to English language articles. The following search term was used ("drug repositioning"(MeSH Terms) OR ("drug"(All Fields) AND "repositioning"(All Fields)) OR "drug repositioning"(All Fields)) OR "drug repurposing"(All Fields) AND ("primary health care"(MeSH Terms) OR ("primary"(All Fields) AND "health"(All Fields) AND "care"(All Fields)) OR "primary healthcare"(All Fields) AND ("off-label use"(MeSH Terms) OR "off-label"(All Fields) OR "off-label use"(All Fields) OR ("off"(All Fields) AND "label"(All Fields)) OR "off label"(All Fields)) AND ("pharmaceutical preparations"(MeSH Terms) OR ("pharmaceutical"(All Fields) AND "preparations"(All Fields) OR "pharmaceutical preparations"(All Fields) OR "medications"(All Fields) Each title and abstract retrieved from the electronic and manual searches independently. The reference list of the included articles was reviewed to identify any other relevant studies. After removing duplicates, articles were identified for further screening using information provided in their title and abstract.

Results: These drugs include some cardiovascular medications, some antidepressants and other drugs including, metformin, hormonal contraceptives, corticosteroids, gabapentin, metoclopramide, colchicine, and sildenafil.

1- Cardiovascular medications

Angiotensin-converting enzyme (ACE) inhibitors and Angiotensin II receptor blockers (ARBs) are antihypertensive medications which can also be used in diabetic patients complicated with microalbuminuria and diabetic nephropathy⁽⁷⁾. Furthermore, losartan, one of the ARBs, showed significant reduction of serum uric acid and can be used safely and effectively in patients with hyperuricemia and gout⁽⁸⁾. Thiazide diuretics are classically used in the management of hypertension and heart failure by reducing salt and water retention. They can decrease urinary calcium excretion which in turn can improve bone density and reduce osteopenic fracture. Therefore, thiazide diuretics are the preferred antihypertensive medication in patients with osteoporosis or nephrolithiasis⁽⁹⁾. Among other medications, nitroglycerin is one of the main preventive and curative medications for acute coronary syndrome. Recently, interesting non-cardiac uses have been discovered. Topical nitroglycerin can be used to treat anal fissure and lateral epicondylitis (tennis elbow). Moreover, transdermal nitroglycerin may be used in diabetic patients with peripheral neuropathy to alleviate pain⁽¹⁰⁾. Spironolactone is an aldosterone antagonist used for refractory hypertension and heart failure with preserved ejection fraction. Due to its anti-androgenic effects, it may be used as adjunctive treatment of hirsutism, acne and female pattern hair loss⁽¹¹⁾. β -blockers are a diverse class of drugs, which have been debatable since their introduction to clin-

ical practice as antihypertensive medications. Other cardiac uses of β -blockers include acute coronary syndrome, cardiac arrhythmias, and heart failure, while the non-cardiac uses include glaucoma, migraine prophylaxis, situational phobia, essential tremors, portal hypertension and adrenergic symptoms of thyrotoxicosis⁽¹²⁾. Aspirin was introduced to the market in 1899 as a pain reliever, anti-inflammatory and anti-pyretic drug. Recently, the guidelines recommended a low dose of 75mg/day of aspirin for the secondary prevention of cardiovascular diseases. However, it is still controversial for primary prevention. Both the American College of Cardiology/American Heart Association (ACC/AHA) and the U.S. Preventive Services Task Force (USPSTF) recommend low-dose of aspirin for primary prevention in patients who have a 10-year cardiovascular risk of at least 10%⁽¹³⁾. For women's health, the USPTF and the American College of Obstetricians and Gynecologists (ACOG) recommended the use of low-dose aspirin to prevent preeclampsia among women at high risk⁽¹⁴⁾. Furthermore, aspirin is claimed to have anti-cancer activity on different malignancies including colon, breast, prostate and lung cancer⁽¹⁵⁾. Calcium channel blockers (CCB) are classified into dihydropyridines (e.g., nifedipine) and non-dihydropyridines (e.g., verapamil). They are approved antihypertensive medications preferred in elderly patients without manifestations of heart failure. Due to their vasodilator effect, they can be used in migraine prophylaxis and treatment of Raynaud's syndrome. Furthermore, verapamil might be associated with improved beta cell function and lower risk of developing diabetes⁽¹⁶⁾.

2- Metformin

Metformin has a long history of challeng-

es. It was synthesized to treat diabetes in the 1920s, discontinued due to claimed toxicity and the low potency compared to insulin, rediscovered in the search for antimalarial agents, repurposed to treat diabetes in the United Kingdom and other European countries in 1958, rejected due to risk of lactic acidosis from other biguanides, and lastly approved in the United States of America in 1995. Recently, metformin has been recommended as the first line oral anti-hyperglycemic drug, because of its proven efficacy and safety⁽¹⁷⁾. It is a unique drug, with multiple therapeutic actions, some of them are still unclear. Reduced cancer risk was indicated in the United Kingdom Prospective Diabetes Study (UKPDS) and has subsequently been demonstrated in many epidemiological studies suggesting that, metformin use was associated with reduced morbidity and mortality of colon, breast, lung and pancreatic cancers⁽¹⁸⁾. This drug has a therapeutic potential for various disorders, especially those linked to hyperinsulinemia and hyperandrogenism including polycystic ovary syndrome (PCOS), human immunodeficiency virus (HIV)-associated lipodystrophy, acanthosis nigricans, hormonal acne and hidradenitis suppurativa. In addition to the former dermatological indications, metformin has shown promising results in treating psoriasis, cutaneous malignancies and hyper-pigmentary disorders⁽¹⁹⁾. The cardio-metabolic effect of metformin has been extensively studied. The American Diabetes Association (ADA) stated that metformin has a neutral or modest weight loss effect on patients with diabetes. In addition, long term use of metformin can reduce the risk of micro and macrovascular complications⁽⁷⁾. A recent meta-analysis of randomized controlled trials suggested that metformin could lower systolic blood pressure, especially among obese patients or those with

impaired glucose tolerance⁽²⁰⁾. The anti-aging effect of metformin is under investigation in a trial called TAME (Targeting Aging with Metformin), enrolling 3000 non-diabetics aged 70–80 years at about 14 centers across the U.S. for 5-7 years follow up⁽²¹⁾. The most recent randomized control trials and systematic reviews on the use of metformin in non-alcoholic fatty liver (NAFLD) concluded that metformin may not improve histological liver fibrosis, but it can improve biochemical and metabolic features related to NAFLD, like body weight, transaminase or cholesterol levels, and HbA1c levels⁽²²⁾.

3- Hormonal contraceptive methods

They contain either progesterone only or combination of estrogen and progesterone, with many available forms to prevent pregnancy. Many studies have discovered other non-contraceptive uses for hormonal birth control methods. They have been approved for treatment of menstrual bleeding disorders, dysmenorrhea and premenstrual syndrome⁽²³⁾. Preparations with antiandrogenic activity are helpful in treating seborrhea, acne, hirsutism and alopecia⁽²⁴⁾. The Royal College of Obstetrician Gynecologists recommends combined pills as a drug of choice for treating symptoms of endometriosis⁽²⁵⁾. Pelvic inflammatory disease (PID) and uterine fibroids have been shown to improve under hormonal contraceptives⁽²⁵⁾. A collaborative reanalysis of data from 45 epidemiological studies including about 23,000 women with ovarian cancer and 87,000 controls in 21 countries showed that the longer the duration of contraceptive use, the more reduction of ovarian cancer. The study estimated that oral contraceptives have prevented about 20000 ovarian cancers and 100000 death from the disease, and the number of cancers prevented will increase up to 30000 cases/year in

the next few decades⁽²⁶⁾. Risk reduction of endometrial cancer is one of the most important health benefits of hormonal contraceptives. A systematic review of 15 case-control studies and four large cohort studies showed 50% risk reduction of endometrial cancer with ever use of combined oral contraceptives. This protective effect persisted for more than 10 years and increases with longer duration of use⁽²⁷⁾. Various studies have reported an inverse relation between oral contraceptive use and the risk of colorectal cancer. A systematic review with meta-analysis of 11 case-control and seven cohort studies showed risk reduction of cancer colon with contraceptive use and this protection is stronger with recent use. Cohort data from the Royal College of General Practitioner's oral contraception study showed that the relative risk for colorectal cancer was 0,72; 95%CI (0.58-0.90) for ever use of combined oral hormonal contraceptives⁽²⁸⁾.

4- Corticosteroids

Despite an incomplete understanding of the mechanism of action, steroids are frequently prescribed for a wide range of diseases, extending from serious life-threatening diseases to non-specific symptoms. Steroids can be life-saving in; patients with anaphylaxis, croup, exacerbated chronic obstructive lung disease (COPD), and exacerbated interstitial lung diseases⁽²⁹⁾. Besides avoiding the triggering factors of allergic conditions, steroids represent the cornerstone management of bronchial asthma, allergic rhinitis and eczema. Moreover, they can be an adjunct treatment in many autoimmune diseases like rheumatoid arthritis and ulcerative colitis⁽³⁰⁾. Many hematological diseases are treated with corticosteroids alone or in combination with chemotherapy (e.g. leukemias, lymphomas, myeloma, ac-

quired hemolytic anemia, aplastic anemia, idiopathic and thrombotic thrombocytopenic purpuras)⁽³¹⁾. The efficacy of steroids in treatment of nephrotic syndrome, lupus nephritis and after renal transplant, is well established⁽³²⁾.

5- Antidepressants

Antidepressants are commonly prescribed in primary care for depression and anxiety. Recently, the use of antidepressants has grown extensively. This can be explained by the prescription for the non-psychiatric conditions and the off-label use. The available evidence suggests that duloxetine can improve quality of life and improve the incontinence episode frequency by about 50% among patients with stress incontinence⁽³³⁾. In relation to women's health, Cochrane reviews reported that selective serotonin reuptake inhibitors (SSRI) are effective in reducing hot flashes and symptoms of premenstrual syndrome⁽³⁴⁾. The European Association of Urology (EAU) guidelines recommends SSRI (dapoxetine) as a first-line treatment for premature ejaculation⁽³⁵⁾. According to the Cochrane database of systematic reviews, bupropion and nortriptyline are effective in improving tobacco withdrawal symptoms⁽³⁶⁾. Regarding the gastrointestinal conditions, a Cochrane review reported that antidepressant could be used as a second or a third line treatment for irritable bowel syndrome⁽³⁷⁾. Specific tricyclic antidepressants (TCA) and selective norepinephrine reuptake inhibitors (SNRIs) are reported to have analgesic effect for chronic painful conditions in which nonsteroidal anti-inflammatory drugs (NSAIDs) are not very efficient⁽³⁸⁾. According to the most recent guidelines, duloxetine, TCA and Venlafaxine are recommended as the first line treatment for diabetic neuropathic pain and fibromyalgia⁽³⁹⁾.

6- Gabapentin

Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA), which has the ability to control epilepsy and postherpetic neuralgia. The mechanism of action by which they exert its clinical effect is still unclear. It is widely used for a number of off-label indications⁽⁴⁰⁾. The most recent guideline of the American college of Chest Physicians recommends gabapentin for patients with unexplained chronic cough⁽⁴¹⁾. A large amount of studies considers a gabapentin trial for primary headache after failure of the first line therapy⁽⁴²⁾. A randomized control trial suggested using gabapentin as an alternative to hormonal replacement therapy to improve hot flashes in postmenopausal women⁽⁴³⁾. According to the latest ADA report, it is recommended as one of the initial treatments for neuropathic pain in patients with diabetes, based on its efficacy and cost⁽⁷⁾. In many clinical trials, gabapentin use was associated with improving symptoms of restless leg syndrome, as well as, sleep and mood outcome⁽⁴⁴⁾.

7- Metoclopramide

A well-known antiemetic drug used widely due to its safety profile, to treat nausea, vomiting, diabetic gastroparesis, and gastroesophageal reflux disease. The use of metoclopramide specifically has been recommended as migraine treatment by the American Headache Society citing "highly likely to be effective"⁽⁴⁵⁾. A recent review showed that metoclopramide is preferred to opioids as the first-line therapy for acute migraine headaches⁽⁴⁶⁾.

8- Colchicine

Colchicine is an old and inexpensive medication with anti-inflammatory properties; but, the exact mechanism of action has not been completely established. Despite

the common gastrointestinal side-effects and the potential for toxicity, it is still the drug of choice for treatment of gout and familial Mediterranean fever⁽⁴⁷⁾. Recently, clinical uses have been expanding to include cardiovascular and dermatological indications. The inflammatory pathway of cardiovascular diseases supports the use of colchicine in treatment of pericarditis and acute coronary syndrome. In dermatology, colchicine is recommended with varying degrees of evidence for Behçet disease, epidermolysis bullosa acquisita, leucocytoclastic vasculitis, Sweet syndrome and recurrent aphthous stomatitis⁽⁴⁸⁾.

9- Sildenafil

A phosphodiesterase-5 inhibitor (PDE5I) was originally investigated to treat angina. However, the cardiovascular effects were not observed, the volunteers reported a surprising side effect of improved erection⁽⁴⁹⁾. PDE5I has been approved for pulmonary hypertension, and might benefit congestive heart failure (CHF), myocardial infarction, altitude sickness, pre-eclampsia and Raynaud's phenomenon⁽⁵⁰⁾. These multiple uses can be explained by its vasodilator effect and complex pathways that involve nitric oxide, cyclic guanosine monophosphate, protein kinase G, extracellular-signal- regulated kinase, B-cell lymphoma protein-2, and Rho kinase inhibition⁽⁵⁰⁾.

Conclusion

Primary healthcare physicians face many challenges in managing patients with multi-morbidity and polypharmacy. To target different diseases with one drug is like catching many birds with one stone. The idea behind drug repurposing is that some drugs can be used to treat other diseases other than the ones they were initially de-

veloped for. The development and approval of drugs is a long and complex process. Drug repurposing may be a safe alternative to reduce cost, improve adherence, decrease drug interactions, and improve quality of life.

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